CLAIMS

1. A hydroxyalkylstarch-protein conjugate, characterized in that the binding interaction between the hydroxyalkylstarch molecule and the protein is based on a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group, or a functional group derived from this aldehyde group by chemical reaction, of the hydroxyalkylstarch molecule and (ii) a functional group, which is able to react with this aldehyde group or functional group derived therefrom of the hydroxyalkylstarch molecule, of the protein, where the bonding resulting directly in the coupling reaction can be modified where appropriate by a further reaction to give the abovementioned covalent bonding.

2. The hydroxyalkylstarch-protein conjugate as claimed in claim 1, characterized in that the functional group derived from the terminal aldehyde group of the hydroxyalkylstarch molecule by chemical reaction is one of the functional groups of a bifunctional linker molecule with which the terminal aldehyde group has been reacted.

3. The hydroxyalkylstarch-protein conjugate as claimed in claim 1 or 2, characterized in that the reactive functional group of the protein is one of the functional groups of a bifunctional linker molecule which has been coupled onto the protein.

4. The hydroxyalkylstarch-protein conjugate as claimed in claim 1 or 2, characterized in that the reactive functional group of the protein has been introduced into the protein by recombinant modification of the original amino acid sequence.

5. The hydroxyalkylstarch-protein conjugate as claimed in claim 1, 3 or 4, characterized in that the covalent bonding is the result of a coupling reaction between a carboxyl group formed by selective oxidation of the terminal aldehyde group, or activated carboxyl group, of the hydroxyalkylstarch molecule and a primary amino group or thiol group of the protein.

6. The conjugate as claimed in claim 5, characterized in that the covalent bonding is an amide linkage which is the result of a coupling reaction between an activated carboxyl group formed by selective oxidation of the terminal aldehyde group of the hydroxyalkylstarch molecule, and a primary amino group of the protein.

7. The conjugate as claimed in claim 1, 3 or 4, characterized in that the covalent bonding is an amine linkage which is the result of a coupling reaction between the terminal aldehyde group of the hydroxyalkylstarch molecule and a primary amino group of the protein to form a Schiff's base, and reduction of the Schiff's base to the amine.

8. The conjugate as claimed in any of claims 1 to 7, characterized in that the hydroxyalkylstarch molecule has a molecular weight in the range from about 4 to about 1000 kD.

9. The conjugate as claimed in claim 8, characterized in that the hydroxyalkylstarch molecule has a molecular weight of about 4 to about 50 kD.

10. The conjugate as claimed in claim 8, characterized in that the hydroxyalkylstarch molecule has a molecular weight of about 70 to about 1000 kD.

11. The conjugate as claimed in claim 10, characterized in that the hydroxyalkylstarch molecule has a molecular weight of about 130 kD.

12. The conjugate as claimed in any of claims 1 to 11, characterized in that the hydroxyalkylstarch molecule has a degree of substitution of about 0.3 to about 0.7.

13. The conjugate as claimed in any of claims 1 to 12, characterized in that the hydroxyalkylstarch molecule has a ratio of C_2 to C_6 substitution of from 8 to 12.

14. The conjugate as claimed in any of claims 1 to 13, characterized in that the hydroxyalkylstarch molecule is a hydroxyethylstarch molecule.

15. The conjugate as claimed in any of claims 1 to 14, characterized in that the protein has a regulatory or catalytic function, a signal transmitting or transport function or a function in the immune response or induction of an immune response.

16. The conjugate as claimed in claim 15, characterized in that the protein is selected from the group composed of enzymes, antibodies, antigens, transport proteins, bioadhesion proteins, hormones and prohormones, growth factors and growth factor receptors, cytokines, receptors, suppressors, activators, inhibitors or a functional derivative or fragment thereof.

17. The conjugate as claimed in claim 15 or 16, characterized in that the protein is α-, β- or γ-interferon, an interleukin, a serum protein, e.g. albumin or a clotting factor, erythropoietin, myoglobin, hemoglobin, a plasminogen activator, BCGF,

BDGF, EGF, FGF, NGF, PDGF, BDNF, CNTF, TGF-α, TGF-β, a colony-stimulating factor, a BMP, somatomedin, somatotropin, somatostatin, insulin, gonadotropin, α-MSH, triptorelin, prolactin, calcitonin, glucagon, a glucagon-like peptide, e.g. GLP-1 or GLP-2, exendin, leptin, gastrin, secretin, an integrin, a hypothalamus hormone, e.g. an ADH, oxytocin, a liberin or statin, a thyroid hormone, e.g. thyroxine, thyrotropin, thyroliberin, a growth hormone, e.g. human growth hormone, LH, FSH, a pigmentary hormone, TNF-α or TNF-β, hirudin, a lipoprotein or apolipoprotein, e.g. Apo-B, Apo-E, Apo-L_a, an oligolysine protein, an RGD protein, a lectin or ricin, bee venom or a snake venom, an immunotoxin, ragweed allergen, antigen E, an immunoglobulin, or a receptor for one of these proteins or a functional derivative or fragment of one of these proteins or receptors.

18. The conjugate as claimed in claim 15 or 16, characterized in that the protein is an enzyme which is selected from an asparaginase, arginase, arginine deaminase, adenosine deaminase, glutaminase, glutaminase-asparaginase, phenylalanine ammonia-lyase, tryptophanase, tyrosinase, superoxide dismutase, endotoxinase, catalase, peroxidase, kallikrein, trypsin, chymotrypsin, elastase, thermolysin, a lipase, uricase, adenosine diphosphatase, purine-nucleoside phosphorylase, bilirubin oxidase, glucose oxidase, glucodase, gluconate oxidase, galactosidase, glucocerebrosidase, glucuronidase, hyaluronidase, tissue factor, a tissue plasminogen activator, streptokinase, urokinase, an MAP kinase, DNAse, RNAse, lactoferrin, and functional derivatives or fragments thereof.

19. A pharmaceutical composition comprising an effective

amount of a conjugate as claimed in any of claims 1 to 18 and a pharmaceutically acceptable carrier and, where appropriate, further excipients and active ingredients.

20. The use of a conjugate as claimed in any of claims 1 to 18 or a composition as claimed in claim 19 for the therapeutic or preventive treatment of humans or animals.

21. A method for preparing a hydroxyalkylstarch-protein conjugate as claimed in any of claims 1 to 18, characterized in that a coupling reaction is carried out in aqueous solution between the terminal aldehyde group, or a functional group derived from this aldehyde group by chemical reaction, of the hydroxyalkylstarch molecule and a functional group, which is able to react with this aldehyde group or functional group derived therefrom of the hydroxyalkylstarch molecule, of the protein, and the bonding resulting directly in the coupling reaction is modified where appropriate by a further reaction.

22. The method as claimed in claim 21, characterized in that the reaction medium of the coupling reaction is water or a mixture of water and an organic solvent, where the water content of the mixture is at least 80%.

23. The method as claimed in claim 21 or 22, characterized in that the terminal aldehyde group of the hydroxyalkylstarch molecule is converted by selective oxidation into the corresponding carboxyl functionality, and the latter is subsequently reacted under activating conditions in aqueous solution with a free amino group of the protein, so that the hydroxyalkylstarch molecule is linked to the protein by an amide linkage.

24. The method as claimed in claim 23, characterized in that the selective oxidation of the aldehyde group is carried out with iodine or metal ions in basic aqueous solution.

25. The method as claimed in claim 23 or 24, characterized in that the coupling reaction is carried out in the presence of a carbodiimide.

26. The method as claimed in claim 25, characterized in that the carbodiimide is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC).

27. The method as claimed in claim 21 or 22, characterized in that the terminal aldehyde group of the hydroxyalkylstarch molecule is coupled to a free amino group of the protein to form a Schiff's base, and the formed Schiff's base is reduced to the amine, so that the hydroxyalkylstarch molecule is linked to the protein by an amine linkage.

28. The method as claimed in claim 27, characterized in that both coupling and reduction take place in aqueous solution.

29. The method as claimed in claim 27 or 28, characterized in that the reducing agent is sodium borohydride, sodium cyanoborohydride or an organic boron complex.

30. The method as claimed in any of claims 27 to 29, characterized in that the coupling and reduction reactions are carried out simultaneously.

31. A method for preparing hydroxyalkylstarch which is selectively oxidized at the terminal aldehyde group,

characterized in that the hydroxyalkylstarch is reacted in a molar ratio of iodine to HAS of from 2:1 to 20:1 in basic aqueous solution.

32. The method as claimed in claim 31, characterized in that the molar ratio of iodine to HAS is about 5:1 to 6:1.

33. The method as claimed in claim 31, characterized in that

a) an amount of hydroxyalkylstarch is dissolved in warm distilled water, and somewhat less than 1 mole equivalent of aqueous iodine solution is added,

b) NaOH solution in a molar concentration which is about 5-15 times that of the iodine solution is slowly added dropwise, at intervals of a plurality of minutes, to the reaction solution until the solution starts to become clear again after the addition,

c) somewhat less than 1 mole equivalent of aqueous iodine solution is again added to the reaction solution,

d) the dropwise addition of the NaOH solution is resumed,

e) steps b) to d) are repeated until approximately 5.5-6 mole equivalents of iodine solution and 11-12 mole equivalents of NaOH solution, based on the hydroxyalkylstarch, have been added,

f) the reaction is then stopped, and the reaction solution is desalted and subjected to a cation exchange chromatography, and the reaction product is obtained by lyophilization.

34. The method as claimed in claim 33, characterized in that the aqueous iodine solution is an approximately 0.05-0.5N iodine solution.

35. The method as claimed in claim 33 or 34, characterized in that the molar concentration of the NaOH solution is about 10 times that of the iodine solution.

36. A method for preparing hydroxyalkylstarch which is selectively oxidized at the terminal aldehyde group, characterized in that the HAS is oxidized in aqueous alkaline solution with a molar excess of stabilized metal ions selected from Cu^{2+} ions and Ag^{+} ions.